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Prognostic implications of left ventricular global longitudinal strain in heart failure patients with narrow QRS complex treated with cardiac resynchronization therapy: a subanalysis of the randomised EchoCRT trial

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ABSTRACT

Objective: Left ventricular (LV) global longitudinal strain (GLS) reflects LV systolic function and correlates inversely with the extent of LV myocardial scar and fibrosis. The present subanalysis of the EchoCRT trial investigated the prognostic value of LV GLS in patients with narrow QRS complex.

Methods and results: LV GLS was measured on the apical 2-, 4- and 3-chamber views using speckle tracking analysis. Measurement of baseline LV GLS was feasible in 755 patients (374 with CRT-ON and 381 with CRT-OFF). The median value of LV GLS in the overall population was 7.9%, interquartile range 6.2-10.1%. After a mean follow-up period of 19.4 months, 95 patients in the CRT-OFF group and 111 in the CRT-ON group reached the combined primary endpoint of.all-cause mortality and heart failure hospitalization. Each 1% absolute unit decrease in LV GLS was independently associated with 11% increase in the risk to reach the primary endpoint (hazard ratio 1.11; 95% confidence interval 95% 1.04-1.17, P<0.001), after adjusting for ischemic cardiomyopathy and randomization treatment among other clinically relevant variables. When categorising patients according to quartiles of LV GLS, the primary endpoint occurred more frequently in patients in the lowest quartile (<6.2%) treated with CRT-ON versus CRT-OFF (45.6% versus 28.7%, P=0.009) whereas no differences were observed in patients with LV GLS ≥6.2% treated with CRT-OFF versus CRT-ON (23.7% versus 24.5%, respectively; P=0.62).

Conclusion: Low LV GLS is associated with poor outcome in heart failure patients with QRS width <130 ms, independent of randomisation to CRT or not. Importantly, in the group of patients with the lowest LV GLS quartile, CRT may have a detrimental effect on clinical outcomes.

Keywords: global longitudinal strain; prognosis; cardiac resynchronization therapy; narrow QRS complex

INTRODUCTION

Cardiac resynchronization therapy (CRT) is an established treatment for heart failure patients with reduced left ventricular ejection fraction (LVEF) and wide QRS complex who remain symptomatic despite optimal medical treatment.[1, 2] The presence of extensive scar tissue in the left ventricle (LV) (in patients with ischemic cardiomyopathy) or significant replacement fibrosis (in patients with non-ischemic cardiomyopathy), however, limits the response to CRT.[3-6] While late-gadolinium contrast enhanced cardiac magnetic resonance (CMR) provides the highest spatial resolution to quantify the extent of scar tissue and fibrosis,[7] echocardiography remains the imaging technique of first choice to evaluate heart failure patients considered for CRT in routine clinical practice. In particular, speckle tracking echocardiography permits assessment of LV global longitudinal strain (GLS), which reflects LV systolic function and inversely correlates with the extent of myocardial scar and fibrosis.[8-10] Since the incremental prognostic value of LV GLS over LVEF has been demonstrated in heart failure patient,[11, 12] LV GLS may be related with prognosis of heart failure patients who underwent CRT implantation.

In 2013, the results of the Echocardiography Guided Cardiac Resynchronization Therapy (EchoCRT) study revealed that CRT does not improve outcome of heart failure patients with a QRS duration <130 ms and LV mechanical dyssynchrony on echocardiography.[13] While the exact mechanism underlying non-response remains elusive, the individual response (based on improvement in clinical symptoms, LV function or prognosis) varied significantly. Intriguingly, the presence and extent of myocardial scar and/or replacement fibrosis may be important for patient outcome. As such, the prognostic value of LV GLS obtained by speckle tracking echocardiography analysis as an indirect marker

of LV myocardial scar and/or fibrosis was analysed in the current substudy of the EchoCRT trial.

METHODS

Study design and patient population

Details of the study design and patient characteristics have been previously reported.[13] In brief, patients (aged 18 years or older) with heart failure symptoms (New York Heart Association class III or IV) despite optimal medical therapy, an LVEF ≤35%, a QRS duration <130 ms, an LV end-diastolic diameter ≥55 mm, echocardiographic evidence of LV dyssynchrony and standard indication for an implantable cardioverter defibrillator (ICD) were randomized to CRT-OFF (control group) or CRT-ON.[13] Patients presenting with acute decompensated heart failure (hemodynamically unstable or need for inotropic support), atrial fibrillation within the previous month or bradycardia requiring pacing, were excluded. The study protocol was approved by the institutional review board of each participating center and all patients gave written informed consent.

Biotronik Lumax HF-T CRT devices with defibrillator function were implanted conventionally with an atrial and right and left ventricular pacing leads.[13] The ICD function was programmed on for all patients. In the CRT-ON group, the device programming was set to optimize the CRT delivery while, in patients allocated to the CRT-OFF group, the device settings were programmed to minimize right ventricular pacing. Device-implanting physicians and physicians involved in the follow-up were aware of the study-group

assignment whereas patients, heart-failure physicians and study personnel completing the follow-up assessments were not.

Echocardiography and global left ventricular longitudinal strain

Transthoracic echocardiography data were acquired according to specific protocol described previously using a uniform ultrasound platform (GE Vivid 7 or E9, Horton, Norway).[13] Off-line echocardiographic data analysis was performed following the American Society of Echocardiography and the European Association of Cardiovascular Imaging recommendations using uniform software (GE EchoPAC version BT11-12, Horton, Norway).[14] Data analysis was performed at a core laboratory (University of Pittsburgh, Echocardiography Core Laboratory, Pittsburgh, PA, USA) by investigators blinded to randomization and all other clinical data. From the parasternal long-axis view, the LV end-diastolic diameter was measured. The LV end-diastolic and end-systolic volumes were measured on the apical 2- and 4-chamber views and the LVEF was calculated according to the Simpson's method. Left ventricular dyssynchrony was assessed with color-coded tissue Doppler imaging data from the apical 4- and 3-chamber views and speckle-tracking echocardiography data from the parasternal mid-ventricular short-axis and quantified as the time difference in peak systolic velocity of two opposing walls and the time difference between peak radial strain of the anteroseptal and posterior segments, respectively.[13]

Global LV longitudinal strain was assessed from 2-dimensional LV apical 4-, 2- and 3-chamber views. The region of interest in each apical view was set by tracing manually the endocardial border. The software displayed automatically an epicardial tracing to include the entire myocardial width. The width of the region of interest could be modified manually to ensure inclusion of the myocardial wall. Subsequently, the software tracked frame by frame

the speckles included in the region of interest and provided a track quality which can be approved or rejected by the observer. The software provides the magnitude of longitudinal strain of 6 segments in each LV apical view and the magnitude of LV GLS strain is calculated as the average of 18 segmental strain values (Figure 1). Global LV longitudinal strain is presented in absolute value. The intraclass correlation coefficient was used to assess the inter- and intraobserver reproducibility from 15 randomly selected patients using the same cine-loop for each view. The intra-class correlation coefficient for LV GLS for intra- and interobserver variability were 0.97 (95% CI 0.93-0.99) and 0.92 (95% CI 0.72-0.98) respectively.

Study endpoint

Patients were followed up for the occurrence of all-cause mortality or hospitalization for worsening heart failure, as reported previously.[13] Additional pre-specified endpoints of the EchoCRT trial included the occurrence of arrhythmias defined by appropriate ICD therapy for ventricular arrhythmias, arrhythmic death and atrial tachyarrhythmia events. These events were adjudicated by an independent committee.

Statistical analysis

The statistical analysis was performed at the Robertson Center for Biostatistics at the University of Glasgow as previously reported.[13] Analyses were performed by intention-to-treat. Continuous variables were presented as mean with standard deviation and compared using two-sample t-tests. Categorical variables were presented as counts and percentages and compared using chi-square tests. To investigate the association of LV GLS with clinical outcome after adjustment for key covariates, Cox proportional hazard models were fitted. Hazard ratios (HRs) and the 95% confidence intervals (CIs) were calculated and adjusted for

randomized treatment group, country, age, gender, ischemic cardiomyopathy, QRS duration, chronic kidney disease, diabetes, LV end-systolic volume, mitral regurgitation grade and LV dyssynchrony measured with speckle tracking echocardiography. To further enhance the clinical value of LV GLS, the study population was divided according to the first LV GLS quartile and randomized treatment (CRT-ON and CRT-OFF). This exploratory analysis permits identification of the subgroup of patients with the worst LV systolic function (lowest LV GLS) and evaluation of their outcome according to the randomized treatment. The time to event curves were estimated with the Kaplan-Meier method and compared with the log-rank test. Follow-up was censored at study closure, date of death, LV assist device implantation, heart transplant or withdrawal from the study or loss to follow-up, whichever came first. The interaction between LV GLS group and randomized treatment group (CRT-ON and CRT-OFF) was tested in a Cox model that included LV GLS group and treatment main effects and interaction terms. All tests were two-sided and a p value<0.05 was considered significant.

RESULTS

Patient characteristics

A total of 809 patients were included, with 405 allocated to the CRT-OFF group (control) and 404 to the CRT-ON group. The present substudy includes 755 patients (374 in the CRT-ON group and 381 in the control group, CRT-OFF) in whom LV GLS analysis was feasible. In 54 patients, LV GLS analysis was not feasible due to image quality. The baseline clinical and echocardiographic characteristics are displayed in Table 1.

Impact of global LV longitudinal strain on prognosis

After a mean follow-up period of 19.4 months, 95 patients in the CRT-OFF group and 111 in the CRT-ON group reached the primary endpoint of all-cause mortality or heart failure hospitalization. On multivariable Cox regression analysis for the pooled study groups, LV GLS as a continuous variable was associated with the occurrence of the primary endpoint with a HR of 1.11 (95% CI 1.04-1.17, P<0.001). Each 1% absolute unit decrease in LV GLS (indicating more myocardial scar/fibrosis) was associated with 11% increase in the risk of all-cause mortality or heart failure hospitalization (Table 2).

Characteristics and outcomes of patients according to global LV longitudinal strain quartile

The median value of LV GLS in the overall population was 7.9%, interquartile range 6.2-10.1%. The study population was categorized into two groups according to the first LV GLS quartile: patients in the lowest LV GLS group (<6.2%) reflecting more myocardial scar/fibrosis and patients with LV GLS ≥6.2%, reflecting less myocardial scar/fibrosis. The baseline characteristics of the patients in the lowest LV GLS group compared with patients with LV GLS ≥6.2% are presented in the supplementary material. The Kaplan-Meier curves show the cumulative event rates of the combined primary endpoint (all-cause mortality or hospitalization for worsening heart failure) for patients divided according to LV GLS <6.2% (more reduced strain) versus ≥6.2% (less reduced strain), reflecting more and less myocardial scar/fibrosis respectively, and the treatment group (CRT-ON versus CRT-OFF) (Figure 2). The interaction between treatment group and LV GLS was not statistically significant; however, as this test was inadequately powered, the prognostic influence of CRT-ON and CRT-OFF on patients with LV GLS<6.2% and patients with LV GLS ≥6.2% was assessed in an exploratory analysis. After a mean follow-up period of 19.4 months, 42 (45.65%) patients with LV GLS <6.2% who received CRT-ON reached the primary endpoint compared

with 27 (28.72%) patients who received CRT-OFF (adjusted HR 2.01, 95% CI 1.19-3.37; P=0.009). In contrast, within the group of patients with LV GLS ≥6.2%, the primary endpoint occurred in 69 (24.47%) and 68 (23.69%) patients treated with CRT-ON and CRT-OFF respectively (adjusted HR 1.09, 95% CI 0.78-1.53; P=0.62). Similar results were observed when focusing only on all-cause mortality (Figure 3).

In terms of arrhythmic events, 34 (8.9%) patients randomized to CRT-OFF and 38 (10.1%) randomized to CRT-ON presented with arrhythmic death or arrhythmic events. LV GLS was not independently associated with this outcome (HR 1.06, 95% CI 0.89-1.25; P=0.51). When comparing patients within the lowest LV GS quartile (<6.2%) versus patients with LV GLS ≥6.2%, similar results were observed: the HRs were similar for both groups of patients (LV GLS<6.2%: HR 1.44, 95% CI 0.56-3.70; P=0.45; LV GLS ≥6.2%: HR 1.09, 95% CI 0.63-1.90; P=0.76).

DISCUSSION

The present substudy of the EchoCRT trial showed that low LV GLS, reflecting larger extent of myocardial scar/fibrosis, is associated with the combined endpoint of all-cause mortality or hospitalization for worsening heart failure after adjusting for key covariates. This association was modulated by the use of CRT: patients with GLS <6.2% who received CRT-ON showed higher risk of the combined endpoint as compared to the other groups.

LV GLS versus cardiac fibrosis and scar formation in heart failure

Myocardial fibrosis is the hallmark of LV remodelling and functional deterioration in heart failure, regardless the underlying etiology.[15] Changes in the extracellular matrix with increase of the collagen production by fibroblasts and myofibroblasts leads to so-called

reactive fibrosis characterized by expansion of the extracellular space. Progressive loss of contractile myofilaments and myocytes apoptosis will lead to replacement fibrosis with accumulation of type I collagen following a localized (e.g. ischemic cardiomyopathy) or diffuse distribution (e.g. inflammatory disease, toxic cardiomyopathy) depending on the etiology. Cardiac magnetic resonance is the most accurate method to non-invasively evaluate reactive and replacement fibrosis. These structural changes lead to regional and global LV dysfunction which can be characterized with speckle tracking echocardiography by measuring myocardial strain. LV GLS reflects the shortening of the myocardial fibers in the longitudinal direction and also has been inversely correlated with the amount of myocardial (diffuse and replacement) fibrosis.[9, 10, 16] In heart failure patients undergoing heart transplantation, LV GLS was significantly correlated with the amount of LV fibrosis on histology (R=0.75, P<0.001).[16] Moreover, in patients with ischemic cardiomyopathy, a good correlation between LV GLS and the amount of scar tissue on late gadolinium contrast enhanced CMR was shown (R=0.62, P<0.001), and a regional value of longitudinal strain <4.5% was the optimal cut-off value to identify transmural scar.[10] These results support these use of LV GLS as surrogate marker of the myocardial fibrosis/scar burden in heart failure patients. However, as demonstrated in other studies,[10, 16] the correlation between the extent of myocardial scar/fibrosis and LV GLS is not straight forward since LV GLS also reflects the LV systolic dysfunction caused by multiple factors such as the workload burden imposed by the scarred segments onto the viable myocardial segments, LV dyssynchrony or loading conditions.

Prognostic value of LV GLS in heart failure patients

Current guidelines include LVEF as a main parameter for risk stratification of heart failure patients.[17] However, accumulating evidence has shown that LV GLS has superior prognostic value over LVEF to predict all-cause and cardiovascular mortality.[11, 12, 18] In a recent study evaluating the prognostic value of LV GLS in 1,065 heart failure patients (43% non-ischemic cardiomyopathy), Sengelov et al showed that each 1% decrease in LV GLS was independently associated with 1.15-fold increased risk of all-cause mortality (P=0.008).[12] Furthermore, LV GLS was particularly useful in risk stratification of patients with LVEF <22%; patients with LV GLS <5.9% showed higher mortality rates as compared with patients with LV GLS≥5.9%. This cut-off value is similar to the lowest quartile of the present population (6.2%). Similarly, patients with LV GLS <6.2% showed worse outcome than their counterparts.

Interaction between LV GLS and CRT

The association between the extent of myocardial scar/fibrosis and CRT efficacy (in terms of improvement in LV systolic function and patients prognosis) has been demonstrated in various studies.[3, 4, 6] In 190 ischemic heart failure patients treated with CRT, those with low scar burden on nuclear imaging with thallium-201 had better prognosis and improvement in LV systolic function as compared to patients with higher scar burden.[3] Similarly, patients with more scar tissue on delayed-contrast enhanced CMR revealed less LV reverse remodelling after CRT.[6]

Two recent studies used LV GLS for prognosis in CRT patients. In a substudy of the Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy trial, patients with higher LV GLS (above the median value ≥8.7%) showed the greatest prognostic benefit from CRT (HR 0.43, 95% CI 0.24-0.77; P=0.005).[19] In a retrospective series

of 205 patients treated with CRT (70% with left bundle branch block QRS morphology), LV GLS <9% was associated with higher rates of all-cause mortality, LV assist device implantation and heart transplantation (unadjusted HR 2.91, 95% CI 1.88-4.49, P<0.001).[20] On multivariate analysis, each decrease in LV GLS was associated with 1.11-fold increased risk of the combined endpoint (95% CI 1.1-1.23, P=0.032).

These results are extended in the current EchoCRT substudy focusing on patients with narrow QRS complex: reduced LV GLS (partially reflecting fibrosis and/or scar formation or severe LV dysfunction) was associated with worse outcome in patients treated with CRT. Two other studies assessed the effect of CRT in patients with narrow QRS complex and scar tissue, although these studies focused on patients with recent infarction.[21, 22] The Prevention of Myocardial Enlargement and Dilation Post Myocardial Infarction (MENDMI) study [21] and the Post-Myocardial Infarction Remodelling Prevention Therapy (PRomPT) trial [22] showed that pacing close to the infarcted area did not prevent LV dilatation or reduced heart failure hospitalization and/or all-cause mortality. The patients included in MENDMI and PROMPT differ significantly from the patients in the EchoCRT trial, who presented with more advanced LV remodelling and higher burden of LV myocardial scar/fibrosis. Nevertheless, these different studies have in common the suggestion that the presence of LV myocardial scar/fibrosis limits the efficacy of CRT. In the EchoCRT population, particularly the patients in the lowest LV GLS quartile (with the largest extent of myocardial scar/fibrosis and lowest contractile function) showed the worst prognosis when treated with CRT-ON, thus suggesting that active LV pacing could have an adverse effect. The pathophysiologic mechanism underlying this association warrants further evaluation.

Study limitations

Although LV GLS was associated with worse outcome in the overall population of the EchoCRT trial after adjusting for key covariates, the interaction term between randomized therapy and LV GLS was not statistically significant probably due to the relatively low number of patients with LV GLS<6.2% and events. However, the present substudy should be considered as hypothesis generating exploring the effect of CRT in patients with significant LV myocardial fibrosis/scar.

CONCLUSION

In heart failure patients with narrow QRS complex, the presence of impaired LV GLS is associated with worse outcome independent of randomisation to CRT or not. Importantly, in the group of patients in the lowest LV GLS quartile, CRT may have a detrimental effect on clinical outcomes.

CONFLICT OF INTEREST

The EchoCRT trial was funded by Biotronik and GE Healthcare; EchoCRT ClinicalTrials.gov number, NCT00683696. Jeroen J Bax disclosed that the department of Cardiology of the Leiden University Medical Center received research grants from Biotronik, Boston Scientific, Medtronic and Edwards Lifesciences. Victoria Delgado received speaker fees from Abbott Vascular and disclosed that the department of Cardiology of the Leiden University Medical Center received research grants from Biotronik, Boston Scientific, Medtronic and Edwards Lifesciences. Peter Sogaard has received grants and personal fees from Biotronik, GE Healthcare and St. Jude medical. Jagmeet P Singh reports personal fees from Biotronik, Boston Scientific, Medtronic, LivaNova and Impulse Dynamics and grants and personal fees

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Table 1. Baseline characteristics of the study population.

	N = 755
Age (years)	58.5±12.5
Male sex – n (%)	547 (72.45)
Ischemic cardiomyopathy – n (%)	413 (54.77)
QRS duration (ms)	105.7±12.68
Walking distance (m)	325.5±121.29
Quality-of-life score	50.7±24.35
NYHA classification – n (%)	
I-II	23 (3.05)
III-IV	732 (96.95)
Hypertension – n (%)	496 (66.31)
Diabetes mellitus – n (%)	300 (39.89)
Chronic kidney disease – n (%)	103 (13.75)
LVESV (ml)	138.8±49.82
LVEDV (ml)	188.0±59.06
LVEF (%)	27.0±5.49
Mitral regurgitation grade – n (%)	
0-2	670 (89.69)
3-4	77 (10.31)
TDI dyssynchrony (ms)	101.2±34.68
Speckle tracking radial dyssynchrony (ms)	217.2±102.28
Global LV longitudinal strain (%)	8.2±2.83

Medication – n (%)	
Beta-blocker	728 (96.42)
ACE inhibitor or ARB	719 (95.23)
Diuretic	650 (86.09)
Aldosterone antagonist	451 (59.74)

Abbreviations: ACE: angiotensin-converter enzyme; ARB: angiotensin receptor blocker; LV: left ventricular; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume; NYHA: New York Heart Association; TDI: tissue Doppler imaging. For continuous variables the mean and standard deviation are presented.

Table 2. Uni- and multivariable Cox proportional hazard models for all-cause mortality or heart failure hospitalization.

	Univariable		Multivariable	
	HR (95% CI)	**P-value**	**HR (95%CI)**	**P-value**
Age (years)	0.99 (0.94-1.05)	0.780	0.98 (0.91-1.04)	0.485
Male gender	0.90 (0.66-1.21)	0.478	0.79 (0.56-1.12)	0.187
Ischemic cardiomyopathy	1.12 (0.85-1.48)	0.427	1.21 (0.87-1.68)	0.251
QRS duration (per 10 ms increase)	1.09 (0.98-1.21)	0.100	1.07 (0.94-1.21)	0.325
Chronic kidney disease	1.68 (1.19-2.38)	0.003	1.34 (0.91-1.96)	0.136
Diabetes mellitus	1.77 (1.34-2.33)	<0.001	1.59 (1.19-2.13)	0.002
LVESV (per 10 mL increase)	1.03 (1.00-1.05)	0.043	1.00 (0.96-1.03)	0.822
Mitral regurgitation grade (3-4)	2.04 (1.38-3.01)	<0.001	1.98 (1.31-2.99)	0.001
Speckle tracking echocardiography radial strain LV dyssynchrony (per 10 ms increase)	1.00 (1.00-1.00)	0.434	1.00 (1.00-1.00)	0.780
Global LV longitudinal strain (per 1% decrease in magnitude)	1.14 (1.07-1.20)	<0.001	1.11 (1.04-1.17)	<0.001

Randomization group CRT-ON	1.26 (0.96-1.66)	0.098	1.19 (0.89-1.58)	0.238

Abbreviations: CI: confidence interval; CRT: cardiac resynchronization therapy; HR: hazard ratio; LV: left ventricular; LVESV: left ventricular end-systolic volume.

Figure 1. Assessment of global left ventricular longitudinal strain with speckle tracking echocardiography. Example of a patient with ischemic heart failure (inferior myocardial infarction). From the apical 4-, 2- and long-axis (APLAX) views, the longitudinal strain curves are displayed for 18 segments. The global longitudinal strain value is calculated as the average of the peak systolic strain of the 18 segments. The bull's-eye plot shows more impaired longitudinal strain in the inferoposterior segments (blue color) concordant with previous inferior myocardial infarction.

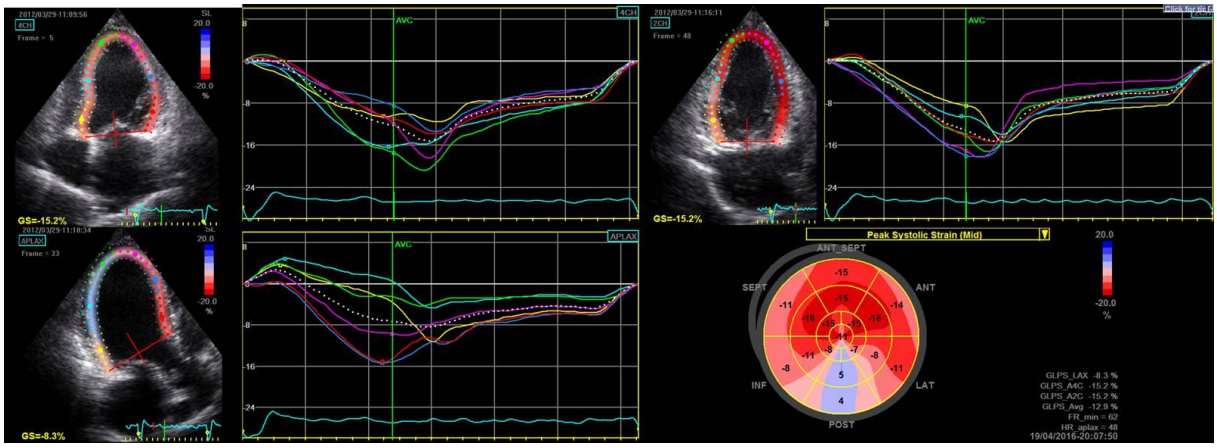
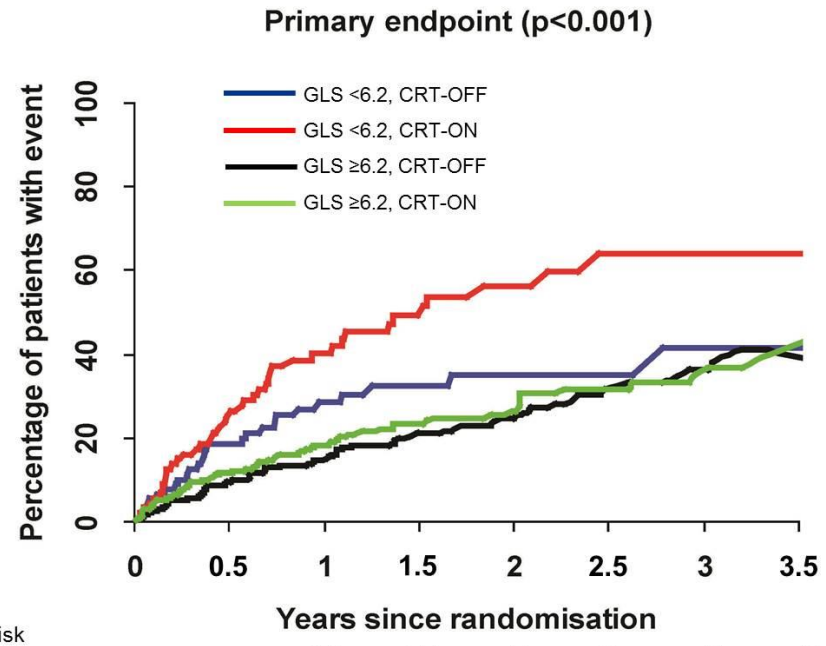
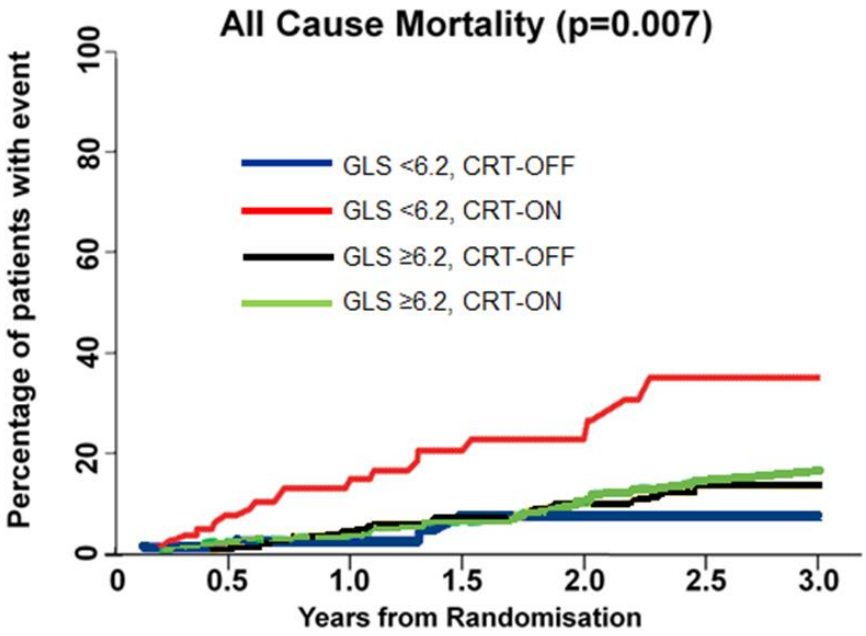


Figure 2. Kaplan Meier estimates for cumulative event rates of the combined primary endpoint (all-cause mortality or hospitalization for worsening heart failure) for patients divided according to the extent global LV longitudinal strain <6.2% (more reduced strain) versus ≥6.2% (less reduced strain) and the treatment group (CRT-ON versus CRT-OFF).



Numbers at risk								
GLS ≥6.2, CRT-OFF	287	226	179	131	94	53	33	10
GLS ≥6.2, CRT-ON	282	213	167	115	76	49	36	16
GLS <6.2, CRT-OFF	94	62	46	26	17	11	6	2
GLS <6.2, CRT-ON	92	58	37	24	14	7	3	2

Figure 3. Kaplan Meier estimates for cumulative event rates of all-cause mortality for patients divided according to the extent global LV longitudinal strain <6.2% (more reduced strain) versus ≥6.2% (less reduced strain) and the treatment group (CRT-ON versus CRT-OFF).



Numbers at risk							
GLS ≥6.2, CRT-OFF	287	246	199	151	108	63	45
GLS ≥6.2, CRT-ON	282	237	197	146	98	64	49
GLS <6.2, CRT-OFF	94	73	58	34	23	14	9
GLS <6.2, CRT-ON	92	71	51	35	20	10	4